AMENDED SPECIFICATION

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PATENT SPECIFICATION

GB 685,696

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COMPLETE SPECIFICATION

Process for the Manufacture of Anti-Histaminic Compounds

We, SCHERING CORPORATION, having a place of business at 2, Broad Street, Bloomfield, County of Essex, State of New Jersey, United States of America, a corporation organized under the laws of the State of New Jersey, United States of America, (Assignee of NATHAN SPERBER, residing in Bronx, County of Bronx, State of New York, United States of America, and DOMENICK PAPA, residing in Brooklyn, County of Kings, State of New York, United States of America, both Citizens of the United States of America), do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to new substances of interesting and important physiological properties and a process for their manufacture. More specifically, the invention relates to the preparation of compounds having pronounced antihistaminic activity.

It is recognized that the liberation of histamine into the tissues, which can be brought about by a multitude of agents or processes, is primarily responsible for many of the allergic manifestations in man. It has been found that certain substances of closely related chemical configurations are effective in alleviating the symptoms of many allergic reactions. The specificity of these chemical substances for the control of allergic reactions is well demonstrated by the researches carried on within the last ten years. However, although the substances prescribed at the present time represent a remarkable advance they exhibit many undesirable side effects, or so-called toxic reactions, among which may be mentioned the high incidence of drowsiness, dizziness, nausea, gastro-intestinal irritation and dryness of the mouth.

In specifications Nos. 307,304 and 646,198 (both as open to public inspection under Section 91 of the Patents Acts 1907—1946) general methods are described for the conversion of ketones of the formula:

$$R^3 . CO . X . NR^1R^2$$

by Grignard reaction into carbinols:

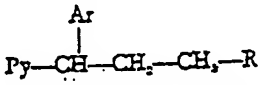
$$\begin{matrix} R_3 \\ R^4 \end{matrix} > C(OH) . X . NR^1R^2$$

and in Specification No. 646,198 for the subsequent replacement of the hydroxyl group by hydrogen, R^1, R^2, R^3 and R^4 being monovalent organic radicals (NR^1R^2 may be a nitrogen ring residue) and X being a divalent linking group. The products are stated to have good musculotropic antispasmodic activity accompanied by low neurotropic antispasmodic activity. In Specification No. 646,198 as open to public inspection under Section 91 *N*-(3-phenyl - 3-*cyclo*hexylpropyl)-piperidinehydrochloride, obtained in this manner from N-piperidylpropiophenone and *cyclo*hexyl bromide, is said to have 12 times the musculotropic antispasmodic activity of papaverine.

We have now found that certain com-

pounds obtainable by similar general reactions possess to an outstanding degree antihistaminic and antianaphylactic activity. Particularly important is the comparative absence of any sedation, dizziness or depression in more than 90% of the cases treated. This advantage is of extreme importance in the clinical application of antihistaminic drugs.

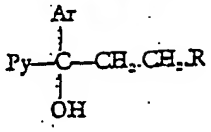
The selected compounds showing this advantage have the general formula



wherein Py stands for 2-pyridyl, Ar for phenyl or an alkyl-, alkoxy-, dialkylamino, chloro- or bromophenyl or for 2-thienyl, and R for a dialkylamino-, piperidino-, pyrrolidino-, or morpholino-group.

Throughout this specification the terms alkyl and alkoxy are used to denote groups having less than seven carbon atoms.

The compounds of the invention are produced by a process comprising the step of condensing a ketone $Ar.CO.CH_2.CH_2.R$, with an organometallic 2-pyridyl compound (e.g. 2-pyridyllithium or 2-pyridyl magnesium halide) to give the carbinol

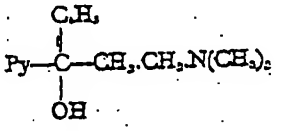


followed by replacement of the hydroxyl group by a hydrogen atom. The resulting bases may be converted into their salts by the usual methods.

Thus from β - dimethylaminopropiophenone (I)

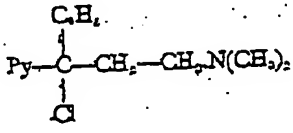
$$C_6H_5.CO.CH_2CH_2.N(CH_3)_2 \qquad (I)$$

there is obtained 1-(2'-pyridyl)-1-Phenyl-3-dimethylaminopropanol-1 (II):



(II)

The carbinol (II) may be reacted with thionyl chloride to form the chloro-compound (III):



(III)

which on reduction with zinc dust and acetic acid gives in good yield the desired 1-phenyl-1-(2'-pyridyl)-3-dimethylaminopropane (IV)

(IV)

By a similar series of reactions compounds in which the phenyl group carries alkyl, alkoxyl, dialkylamino, chlorine or bromine substituents may be prepared. For the *p*-chloro-compound, for example the starting material is the ketone

p-$Cl.C_6H_4.CO.CH_2.CH_2.N(CH_3)_2$,

obtained by the Mannich reaction from *p*-chloroacetophenone, dimethylamine and formaldehyde.

By using diethylamine, piperidine, pyrrolidine or morpholine in place of dimethylamine the corresponding diethylamino-, piperidino-, pyrrolidino- or morpholino- ketone may be prepared.

The compounds of the invention may be used in the form of the free bases or in the form of the salts thereof with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids and organic acids, such as salicylic, tartaric, maleic, succinic, citric and lactic acids.

Typical examples of salts of the 3-phenyl-3-(2-pyridyl)-N,N - dimethypropylamine of Example I are the following:

1. The mono-hydrochloride is obtained by passing anhydrous hydrogen chloride into an ether solution of the γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine. The hydrochloride can be recrystallized from absolute alcohol and absolute ether and melts at 117—119° C.

2. The tartrate of the compound of Example I is obtained in the usual manner and melts at 114—115° C.

3. The mono-hydrogen oxalate is prepared in ethanol and after recrystallization from acetone melts at 152—152.5° C.

4. The mono-hydrogen succinate is prepared in a manner similar to the mono-hydrogen oxalate in ethyl alcohol solution and after recrystallization from pentanol melts at 99.5—100° C.

5. The mono-hydrogen maleate is similarly prepared and after recrystallization from pentanol, melts at 106—107° C.

The compounds may be used in a variety of forms such as tablets for oral administration, creams for topical application, and injectible solutions. Preferably the salts of the compounds are used in the creams which may be of the usual formulations. The injectible solutions comprise non-toxic salts.

EXAMPLE I.

1-Phenyl-1-(2'-pyridyl) - 3 - dimethylaminopropane.

The intermediate carbinol, phenyl - (2'-

pyridyl)-β-dimethylaminoethylcarbinol (II), is prepared as follows:

β-Dimethylaminopropiophenone hydrochloride (0.1 mole) is dissolved in 50 cc. of water and cooled in an ice-bath. The free base is liberated with ice and 10% sodium carbonate solution, and the oil is taken up in ether. The ether layer is washed with water and dried over anhydrous potassium carbonate. Upon removal of the ether, the free base is obtained.

A solution of 0.2 moles of 2-pyridyllithium in 250 ml. of ether is prepared and after cooling to −40° C., a solution of 18 g. of β-dimethylaminopropiophenone in 50 cc. of ether is added dropwise with stirring over a period of ½ hour. Upon completion of the reaction, the temperature is allowed to rise to −15° C. and the reaction mixture is stirred at this temperature for one hour. The contents of the flasks are decomposed with ice and hydrochloric acid and then made basic with gaseous ammonia. The resulting oil is taken up in ether, the ether evaporated and the residue distilled. The carbinol is a viscous, yellow syrup, boiling at 176—180° C./2 mm.

The carbinol (II) is converted to the propylamine as follows:

Phenyl-(2'-pyridyl) - β - dimethylaminoethyl carbinol (II) (0.1 mole) is dissolved in 250 cc. of dry benzene and thionyl chloride (0.15 mole) added, keeping the temperature between 0 and 10° C. The reaction is allowed to come to room temperature, stirred for an additional ½ hour, and then made basic with a dilute solution of sodium hydroxide. The benzene layer is separated, dried and concentrated *in vacuo* leaving a viscous, purple oil. The crude phenyl-(2'-pyridyl)-β-dimethylaminoethyl-methylchloride is dissolved in 200 cc. of glacial acetic acid and zinc dust (0.3 mole) added. The reaction mixture is stirred and heated on the steam bath for 6 hours, the zinc salts filtered and the filtrate concentrated *in vacuo*. The thick syrup is made alkaline with dilute sodium hydroxide and the oil which separates is extracted with ether. The ether layer is dried, concentrated and the residue distilled.

EXAMPLE II.

1(*p*-Methoxyphenyl)-1-(2' - pyridyl) - 3-dimethylaminopropane.

This compound is prepared by the procedure described in Example I using *p*-methoxyacetophenone in a Mannich condensation with formaldehyde and dimethylamine hydrochloride to prepare β-dimethylamino-*p*-methoxypropiophenone. The latter is then carried through the series of reactions described in Example I. The substituted propylamine is a pale yellow, viscous liquid; b.p. 172—175° C./1.5 mm.

EXAMPLE III.

1(*p*-Chlorophenyl)-1-(2'-pyridyl)-3-dimethylaminopropane.

Using *p*-chlorophenylacetophenone in the Mannich reaction followed by the 2-pyridyllithium reaction and the series of reactions described in Example I the corresponding propylamine is prepared; b.p. 139—141° C./1.0 mm.

EXAMPLE IV.

1-(Phenyl)-1-(2'-pyridyl)-3-diethylaminopropane.

By substituting β-diethylaminopropiophenone hydrochloride for the dimethylamino compound in Example I there is obtained the compound of this example; b.p. 156—157° C./2.0 mm.

EXAMPLE V.

1-(Phenyl)-1-(2'-pyridyl)-3-N - piperidinopropane.

By substituting piperidine hydrochloride for dimethylamine hydrochloride in Example I, the piperidino compound is obtained as a viscous yellow liquid boiling at 176—177° C/3.5 mm.

EXAMPLE VI.

1-Phenyl-1-(2'-pyridyl)-3-(N-pyrrolidyl) propane.

The β-(1-pyrrolidyl)propiophenone is obtained by the Mannich condensation of acetophenone with formaldehyde and pyrrolidine. The free base is liberated from the hydrochloride and then is reacted with 2-pyridyllithium, followed by further reactions in accordance with the procedure of Example I. The pyrrolidylpropane is obtained as a pale yellow oil boiling at 164—166° C./2—3 mm.

EXAMPLE VII.

1-(*p*-Chlorophenyl)-1-(2'-pyridyl)-3-(N-pyrrolidyl)propane.

This compound is obtained exactly as described for the unsubstituted compound of the above example using *p*-chloroacetophenone in place of acetophenone. The halogenated compound of this example is a yellowish liquid boiling at 175—177° C./1—2 mm.

The following are other typical amines prepared by the methods of the invention:

1-(2'-Thienyl)-1-(2''-pyridyl)-3 - dimethylaminopropane, b.p. 154° C./2 mm.

1-(*p*-Methylphenyl)-1-(2'-pyridyl) - 3 - dimethylaminopropane, b.p. 137—140° C./0.5 mm.

1-(4' - Dimethylaminophenyl) - 1 - (2''-pyridyl)-3-dimethylaminopropane, b.p. 183—185° C./1.5 mm.

1-(2',3'-Dimethoxyphenyl)-1 - (2''-pyridyl)-3-dimethylaminopropane, b.p. 195—200° C./1—2 mm.

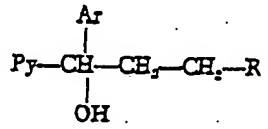
1-(*p*-Isopropylphenyl)-1-(2' - pyridyl) - 3-dimethylaminopropane, b.p. 147—152° C/1.0 mm.

What we claim is: —

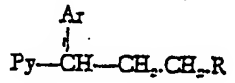
1. The step in the production of pyridyl aliphatic amines and their salts which consists in reacting a ketone of formula

$$Ar.CO.CH_2.CH_2.R$$

wherein Ar stands for phenyl or for an alkyl-, alkoxy-, dialkylamino-, chloro- or bromophenyl and R stands for a dialkylamino-, piperidino-, pyrrolidino- or morpholino-group, with an organometallic 2-pyridyl compound (e.g. 2-pyridyllithium or 2-pyridyl magnesium halide) to give the carbinol

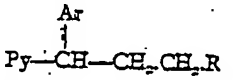


wherein Py stands for 2-pyridyl followed by replacement of the hydroxyl group in the resulting carbinol by hydrogen to give the compound



and conversion of the product, if desired, into its salts.

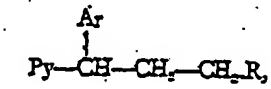
2. The step in the production of pyridyl-aliphatic amines and their salts as claimed in Claim 1 comprising the conversion of the carbinol into the corresponding halide, e.g. by the action of thionyl chloride and replacement of the halogen by hydrogen, e.g. by reduction with zinc dust and acetic acid, to give a compound of formula



and conversion of this product if desired, into its salts.

3. The steps as claimed in either of the preceding claims in which Ar stands for phenyl or p-chlorophenyl and R for dimethylamino or N-pyrrolidyl.

4. Process for the production of saturated compounds of the formula



substantially as described with reference to each of the foregoing Examples.

5. 3-(2¹-Pyridyl)-3-arylpropylamines, whenever produced by the process claimed in any of the preceding claims.

6. Salts of 3-(2¹-pyridyl)-3-aryl-propylamines whenever produced by the process claimed in any of Claims 1—3.

Dated this 13th day of October, 1949.

URQUHART-DYKES & LORD,
Maxwell House, 11, Arundel Street, Strand,
London, W.C.2, and
12, South Parade, Leeds 1,
Chartered Patent Agents.

Reference has been directed in pursuance of Section 9, sub-section (1) of the Patents Act, 1949 to Patent No. 689,234.

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